

matter. Reexamination and reconsideration of the application, as amended, are requested.

A. Section 112, Second Paragraph rejection addressed

Claims 1-26 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that "[t]he expression, 'a method for preventing lesions caused by a virus of Herpesviridae or Poxviridae . . . ' in claim 1, line 1-2, renders the claims indefinite" because "[e]xamples of how and when to prevent viral lesions caused by [sic] are not set forth in the specification". The Examiner further states that he would favorably consider the term "prohylaxis" over "prevention." This rejection is respectfully traversed.

The Examiner's attention is directed to paragraph [0048] of the Specification, which states in part that

"when the same composition was applied within 24 hours of the prodromal stage of infection, that is, during awareness of burning, tingling, or itching but before blister development, the subjects noted that development of a papule did not occur. Thus, the compositions of the invention appear to prevent the formation of lesions".

The Examiner's attention is further directed to paragraph [0064] of the Specification, which states

"[w]hen the same composition was applied within 24 hours of awareness, i.e., burning tingling or itching, further development did not occur. The usual edema and pain accompanying herpes eruptions was eliminated."

It is therefore asserted that the claims are definite and clearly define the metes and bounds of the invention. However, in an effort to expedite prosecution, claims 1, 17 and 26 have been amended herein to replace the phrase "a method for preventing" with "a method for the prophylaxis" in accordance with the Examiner's suggestion. Withdrawal of this rejection is respectfully requested.

B. Section 103(a) Rejections addressed

Claims 1-26 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Pamukoff, Poli *et al.*, Bhatia *et al.* and Simmons *et al.* The Examiner states that while the references do not expressly teach the employment of 1-10% ethyl alcohol or 1,4-butanediol

and glycolic acid or hydrochloric acid into the same method of inactivating viruses, it would have been obvious to one skilled in the art to employ 0.6% glycolic acid or hydrochloric acid and 1-10% ethyl alcohol or 1,4-butanediol and adjust the final pH to 2.45 in a method of inactivating viruses, because these agents are known to be useful to inactivate viruses individually. This rejection is traversed.

The Examiner relies on *In re Kerkhoven* to support the position that combining two or more agents which are known to be useful to formulate an antiviral composition individually into a single composition useful for the very same purpose is *prima facie* obvious. However, this rejection is based on the false premise that the art shows that each element of the composition used in the claimed methods is known to be an antiviral agent, and therefore this rejection lacks foundation.

Further, to establish a *prima facie* case of obviousness, it is well established that the prior art relied upon must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references (*In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988; *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992). Second, the proposed modification of the prior art must have had a reasonable expectation of success (*Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. It is asserted that the Examiner has not met this burden and therefore has not established a *prima facie* case of obviousness.

Independent claim 1 as amended herein is directed to a method for the prophylaxis of lesions caused by a virus of the Herpesviridae or Poxviridae family, comprising topically applying a composition consisting essentially of:

- 0.2-30% by volume of a C1-C3 alcohol or a C2-C4 diol, and
- a sufficient amount of an acid to adjust the pH of the composition between 2.45 and 4.6.

The methods of the present invention utilize compositions containing ingredients, i.e., a low concentration of a lower chain alcohol and an acid, which by themselves are not potent antivirals when applied topically to the site of infection, but which produce a **synergistic** antiviral effect when used in combination at a pH between 2.45 and 4.6 as required for the methods of this invention.

As support for the synergistic effect of the components of the claimed composition, submitted herewith are several references as "Exhibit A" providing evidence that low concentrations of lower chain alcohols alone do not have virucidal activity. For example, U.S. Patent No. 5,591,442 to Diehl *et al.* states at column 1, lines 22-27 that "known compositions with antiseptic action are highly volatile alcohols. However, high alcohol concentrations must be present for effectiveness . . . The alcohol content is generally more than 50, mostly about 60 to 80% by wt." (emphasis added). See also column 2, lines 15-20 which states "in view of the synergistic effect of the alkyl alcohol component and the glycerol monoalkyl ether, it is possible to reduce the alkyl alcohol content." Thus, Diehl *et al.* demonstrated that a synergist must be added to the alcohol in order for lower concentrations of the alcohol to have virucidal activity.

As another example, U.S. Patent No. 6,080,417 to Kramer *et al.* (see Exhibit A) states at column 1, lines 10-18 that "increasingly, the viral effectiveness of hand disinfectants based on alcohol has lately been discussed . . . it is known that polio viruses for instance can be inactivated only with a very high percentage of ethanol, and so the usual concentration of between about 70 and 80 weight % is not adequate for this purpose" (emphasis added). Kramer *et al.* further state at lines 43-50 of column 1 that "it has been found that . . . preparations that have a substantially lower alcohol content in the form of lower alcohols can also be used, if they contain mixtures of synergists" (emphasis added). Thus, Kramer *et al.* also demonstrated that a synergist must be added to the alcohol in order for lower concentrations of the alcohol to have virucidal activity.

As yet another example, Kurtz *et al.* (J. Hospital Infection; see Exhibit A) assayed several lower chain alcohols against the rotavirus and observed that antiviral activity was obtained only when the alcohol concentration was at least 30-50% (see page 323 and Table 1). Further, *in vitro* assays against the echovirus showed that the alcohol concentration must be greater than 50% (see the first paragraph of page 324).

The Examiner's attention is also directed to von Rheinbaben *et al.* (U.S. Patent No. 5,728,404; submitted in a previously filed Information Disclosure Statement). von Rheinbaben *et al.* found that compositions comprising between 40-80% by weight of ethanol, n-propanol, isopropanol, butanol, or mixtures thereof were ineffective against polio, adeno, vaccinia, and SV40 tumor viruses; however, these compositions could be made virucidal by adding at least one metal salt to these alcoholic compositions.

It is believed that sufficient evidence in the form of the above-discussed references

has been made of record in support of the fact that low concentrations of lower chain alcohols by themselves are ineffective in inactivating viruses both *in vitro* and *in vivo*.


The Examiner's attention is also directed to the data presented in Table 2 of the present invention, which demonstrates that glycolic acid alone is virucidally effective when at a pH at or below 4.0, but is ineffective at higher pH's.

As further support of the unexpected and supra-additive effects obtained with the compositions used in the claimed methods, submitted herewith is a Rule 132 Declaration by Jack Konowalchuk. The data provided in the Rule 132 Declaration show that when low concentrations of ethanol (e.g., 1-10%) are combined with glycolic acid at a pH between 2.5 and 4.5, the compositions have virucidal activity. However, when the pH is at 4.5 or above, the compositions have little or no virucidal activity. As stated in the Declaration, given that lower chain alcohols at low concentrations are not virucidal and acid solutions above pH 4.5 are not virucidal, a synergistic effect is unquestionable when a combination of these agents provides an effective virucidal composition.

In summary, it has been demonstrated that alcohols at low concentrations (e.g., below 30%) are not virucidal, and further that glycolic acid at pH 4.0 or above is not virucidal. The data provided in the present application and the Rule 132 affidavit demonstrate the surprising and unexpected result that a composition consisting essentially of a combination of a low concentration of alcohol (0.2-30%) and an acid, wherein the pH of the combination is adjusted to between 2.45 and 4.6, can prevent lesions caused by a virus of the Herpesviridae or Poxviridae family. Accordingly, a synergistic effect must be assumed.

The Examiner clearly has not considered the invention in its entirety. The Examiner has not provided any evidence that suggests that an inflammation or lesion caused by a virus can be prevented by contacting applying a composition consisting essentially of a low concentration of an alcohol and an acid to a site of a potential lesion. Further, the Examiner has not provided any evidence that the pH of this composition is critical to its virucidal activity. Also, the Examiner has not provided evidence that it was known that the elements of the compositions used in the methods of this invention would demonstrate synergistic effects. The Examiner has merely presented references that contain the assorted features of the invention. However, the burden is on the Examiner to show why it would appear that the references would have been combined. *In re Fritch, supra*.

The Examiner relies on Pamukoff for teaching a 1-10% ethanol-containing composition for treating viral infections. However, the Pamukoff reference is misleading



and, as demonstrated above, is an improper reference. Pamukoff teaches a method for treating viral infections by applying to the external site of the infection a composition comprising glycerine, ethyl alcohol, and an alkali metal halide salt. However, contrary to the Examiner's assertion, Pamukoff did not provide evidence that ethanol alone has virucidal activity, but rather demonstrated that ethanol was effective only when combined with an alkali metal halide salt and glycerine. However, as discussed above, the art is replete with evidence that low levels of lower chain alcohols alone have little or no antiviral activity.

Also as discussed above, von Rheinbaben *et al.* and Diehl *et al.* have clearly demonstrated that the virucidal activity of Pamukoff's composition was due to the combination of the ethanol with glycerine and/or the metal halide salt, which contradicts the Examiner's assertion that Pamukoff teaches that 1-10% ethanol alone is virucidal. Thus, the Examiner's assertion that Pamukoff teaches one of the virucidal components of the invention is wrong. Pamukoff does not teach that ethanol is a virucidal agent, but rather teaches a virucidal composition which must contain the ethanol, the metal salt and glycerine in order to be virucidal. The "consisting essentially of" language of the present claims specifically excludes a metal salt and glycerine.

Further, there is no suggestion in Pamukoff that the addition of an acid to his composition would provide a virucidal composition that could be used to prevent an inflammation or lesion caused by a virus. Consequently, persons skilled in the art and knowledgeable in the above-described art disputing the effectiveness of low concentrations of lower chain alcohols and diols as an effective antiviral agents, would not have been motivated or guided by Pamukoff to arrive at the claimed methods.

Contrary to the Examiner's assertion, the prior art provides no motivation to combine the teachings of Pamukoff with the teachings of the other references to arrive at the methods of the present invention. Thus, there is no reason why one would add an acid to the composition used in Pamukoff's method. Further, since Pamukoff states that his composition is already effective, there is no suggestion or motivation to modify the compositions or method of Pamukoff by adding an acid as suggested by the Examiner. "Without some incentive or suggestion in the prior references to use materials disclosed in the referenced in the manner claimed by a patent applicant, a rejection of applicant's claimed invention is improper." *Ex parte* Shepard and Gushe, 188 USPQ 536 (PTO Bd. App. 1974); *In re* Samour, 197 USPQ 1 (CCPA 1978).

The Examiner then relies on Poli *et al.* for teaching that glycolic acid is virucidal

against herpesvirus. Poli *et al.* describe a study to determine the *in vitro* antiviral activity of certain organic acids. Poli *et al.* found that certain organic acids have antiviral activity, and that this activity was found to be proportional to the polarity of the molecule (page 255, last paragraph). However, Poli *et al.* do not teach or even suggest that the pH of the acid solution is critical for virucidal activity. Further, Poli *et al.* do not teach or even suggest a method of treating an inflammation or lesion caused by a virus using a composition consisting essentially of a low concentration of a lower chain alcohol and an acid at a specific pH. Thus, there is no motivation or suggestion by Poli *et al.* to combine the acids disclosed by Poli *et al.* with the composition of Pamukoff.

As discussed above, the present invention has demonstrated a synergistic effect between the alcohol, acid, and pH elements of the claimed methods. That is, the inventors discovered that lower chain alcohols at low concentrations can be effective in preventing an inflammation or lesion caused by a virus when used in combination with an acid and at a pH between 2.45 and 4.6. These surprising and unexpected results are not taught or even suggested by Poli *et al.* Accordingly, there is no motivation to combine the teachings of Poli *et al.* with the other cited references. It is not enough that the Examiner present references that contain the assorted features of the invention. The burden is on the Examiner to show why it would appear that the references would have been combined. *In re Fritch, supra*.

The Examiner then relies on Bhatia *et al.* for teaching that 0.4 N hydrochloric acid is effective in the inactivation of sheep pox virus. The purpose of Bhatia *et al.* was to determine if hydrochloric acid would inactivate the goat-pox virus *in vitro* **prior** to contacting the acid with the goats' skin. Bhatia *et al.* disclose a method of combining goat-pox virus with hydrochloric acid and incubating this suspension for a period of time (see page 518, second column, last paragraph). In order to determine if the virus was still active after incubation with acid, Bhatia *et al.* injected the suspension under the goats' skin and watched for signs of pain at the injection site.

Thus, the composition of Bhatia *et al.* is actually a mixture of the goat-pox virus and a concentrated acid. Further, Bhatia *et al.* only demonstrate that acid kills a virus *in vitro*. Bhatia *et al.* do not teach or even suggest applying acid to the skin to prevent an inflammation or lesion caused by a virus of the Herpesviridae or Poxviridae family. More importantly, Bhatia *et al.* do not teach or even suggest a method of preventing an inflammation or lesion caused by a virus by applying to the inflammation or lesion a composition consisting essentially of 0.2-30% by volume of a C1-C3 alcohol or C2-C4 diol and an acid, wherein the

pH of the mixture is between 2.45 and 4.6. Accordingly, there is no motivation to combine the teachings of Bhatia *et al.* with the other cited references. Again, it is not enough that the Examiner present references that contain the assorted features of the invention. The burden is on the Examiner to show why it would appear that the references would have been combined.

In re Fritch, supra.

Finally, the Examiner relies on Simmons *et al.* for teaching that 1,4-butanediol is useful in an antiviral method against HIV infection. The Examiner has misinterpreted the reference and therefore the use of this reference in a Section 103 rejection is misguided.

Simmons *et al.* teach a cold chemical sterilant comprising a monohydric alcohol, a polyhydric alcohol, a saturated dialdehyde and a cationic surface-active agent (see column 11, lines 22-25). Simmons *et al.* further state at column 13, lines 33-40 that "[t]he specific monohydric alcohols, polyhydric alcohols, gluteraldehyde and cationic surface active agent and relative ratios complement and interact synergistically to create the desired solubility . . . required for the effective use of the cold chemical sterilant against the challenge" (emphasis added). Thus, it is clear that Simmons *et al.* do not teach that 1,4-butanediol alone is useful in an antiviral method against HIV infection. Rather, they teach that their method for sterilizing instruments must use a composition containing all of the above-listed components.

More importantly, there is no suggestion in Simmons *et al.* to add an acid in a sufficient amount to adjust the pH of the solution to between 2.45 and 4.6 to product a more effective antiviral composition. In fact, Simmons *et al.* actually teach away from using an acid. See column 14, lines 3-8, which states "[i]n order to accomplish the design criteria of a hypocompatible biodegradable nonaqueous cold chemical sterilant effective against the wide range of pathogenic target organisms described herein, the composition should have a pH of between about 6.0 and 7.5 or essentially neutral" (emphasis added). Accordingly, Simmons *et al.* do not provide the requisite motivation to prevent inflammations or lesions caused by a virus using a composition consisting essentially of a low concentration of an alcohol and an acid, wherein the composition has a pH between 2.45 and 4.6. Therefore, the Examiner has failed to provide a reason why one skilled in the art would have found any incentive to combine the teachings of Simmons *et al.* with any or all of the other art cited by the Examiner to arrive at the claimed methods.

The Examiner states at the bottom of page 4 of the final Office Action that the optimization of a results-effective parameter is obvious, absent evidence to the contrary. However, the Examiner is reminded that a particular parameter must first be recognized as a

variable which achieves a recognized result before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re* Antoine, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant case, the Examiner has not provided evidence in the cited art that the pH of a composition consisting essentially of 0.2-30% by volume of a lower chain alcohol and an acid is critical in determining the virucidal activity of the composition. In fact, the Examiner has not even shown a method of preventing inflammations or lesions caused by a virus, comprising topically applying a composition consisting essentially of 0.2-30% by volume of a lower chain alcohol and an acid, regardless of the pH or virucidal activity. Therefore, the Examiner's comment regarding optimization of variables is immaterial.

For the reasons presented above, the methods of the present invention, considered as a whole as required by Section 103, would not have been *prima facie* obvious to one skilled in the art at the time this invention was made. Withdrawal of the obviousness rejection of claims 1-26 is respectfully requested.

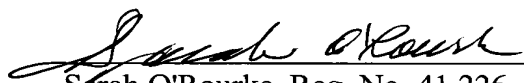
CONCLUSIONS

All of the remarks in the final Office Action have been addressed, claims 1-26 are believed to be in condition for allowance, and such action is respectfully requested. No fee is believed to be due as a result of the filing of this Amendment. However, the Examiner is authorized to charge any fee deficiency associated with this response to Deposit Account No. 50-1123.

The Examiner is asked to kindly contact the undersigned by telephone should any outstanding issues remain.

Respectfully submitted,

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MARKED-UP VERSION SHOWING CHANGES MADE TO SPECIFICATION

Please amend paragraph [0012] as follows:

Konowalchuk et al. reported a 1000-fold reduction in poliovirus infectivity after incubation with grape juice, at the natural pH of the wine (pH 3.3-4.4) or at pH 7.0 for 24 hours at 4° C, and found that commercial grape juice at neutral pH inactivated the herpes simplex virus. Red wines were reported to be more antiviral than white wines. The effect of wine at its natural pH against the herpes [simples] simplex virus was not examined.

Please amend paragraph [0014] as follows:

Von Rheinbaben, *et al.* (U.S. Patent No. 5,728,404) disclose compositions having virucidal activity against "naked" viruses (e.g., polio, adeno, vaccina, and SV40 tumor virus) comprising 50% to 90% by weight of at least one member selected from the group consisting of C₁-C₄ aliphatic monohydric alcohols and from 0.1% to 1.0% by weight of at least one metal salt, such as a zinc salt. Von Rheinbaben *et al.* found that compositions comprising between 40-80% by weight of ethanol, n-propanol, isopropanol, butanol, or mixtures thereof [that] were ineffective against polio, adeno, vaccinia, and SV40 tumor viruses; however, these compositions could be made virucidal by adding metal salts to these alcoholic compositions.

Please amend paragraph [0026] as follows:

Accordingly, one aspect of this invention provides virucidally effective compositions [comprising] consisting essentially of an aqueous solution of a short chain alcohol or diol adjusted to a pH at or below 4.6 with a suitable acid. Such compositions suitable for topical application and nasal deliverable form are also provided.

Please amend paragraph [0034] as follows:

The compositions of this invention [comprising] consist essentially of a dilute aqueous solution of a C₁ to C₃ monohydroxy alcohol or a C₃ to C₄ diol which has been adjusted to a pH of 4.6 or below by the addition an inorganic or an organic acid. As used herein, "C₁," "C₂," "C₃," and "C₄" refer to alcohols having one, two, three, or four carbons, respectively. Such alcohols may be straight chain or branched alcohols. In one embodiment,

the compositions are buffered, preferably with a suitable buffer that will maintain the pH of the composition. Such buffers are well known to persons skilled in the art.

Please amend paragraph [0038] as follows:

In one embodiment, a composition of this invention [comprises] consists essentially of 10% by volume of 95% ethanol in water, wherein the pH of the composition is adjusted to a pH of 4.6 or below by the addition of glycolic acid or HCl. For example, the pH may be adjusted to 4.6 by the addition of a 0.6% aqueous glycolic acid solution or a 0.1M HCl solution.

Please amend Table 3 on page 10 as follows:

Table 3: Upper pH limit at which HSV-1 is inactivated by the alcohol

Alcohol	Concentration of alcohol	Upper limit of pH
methanol	0.2%	4.6
ethanol	[0,2%] <u>0.2%</u>	4.4
n-butanol	[0,2%] <u>0.2%</u>	4.6
1,2-butanediol	0.2%	4.2
2,3-butanediol	0.2%	4.6

Please amend paragraph [0048] as follows:

The compositions were evaluated for the treatment of recurrent oral-facial herpes simplex infections as described in Example 2. A group of patients applied a solution [comprising] consisting essentially of 10% by volume of 95% ethanol and 0.6% by weight glycolic acid in water, adjusted to pH 2.45, at the time of erythema, papule or vesicle stages. Development of blisters was arrested and rapid crusting of the vesicles occurred within 2 to 3 days of treatment, as compared to 10 or more days without treatment. When the same composition was applied within 24 hours of the prodromal stage of infection, that is, during awareness of burning, tingling, or itching but before blister development, the subjects noted that development of a papule did not occur. Thus, the compositions of the invention appear to prevent the formation of lesions, as well as being effective in reducing the healing time of the lesions.

MARKED-UP VERSION OF AMENDED CLAIMS

Please amend claims 1, 17 and 26 as follows:

1. (Amended) A method for [preventing] the prophylaxis of lesions caused by a virus of the Herpesviridae or Poxviridae family, comprising topically applying a composition consisting essentially of 0.2 to 30% by volume of a C1, a C2, or a C3 alcohol or a C2, C3, or C4 diol, and a sufficient amount of an acid to adjust the pH of the composition to between 2.45 and 4.6 [or less], wherein said composition is applied during symptoms of pain, itching burning, or tingling.
17. (Amended) A method for [preventing] the prophylaxis of lesions caused by a virus of the Herpesviridae or Poxviridae family, comprising topically applying a composition consisting essentially of 0.2 to 30% by volume of an alcohol selected from the group consisting of methanol, ethanol, 1-propanol, 2-propanol, 2,3-butanediol, 1,2-butanediol, 1,3-butanediol, and 1,4-butanediol, and a sufficient amount of an acid to adjust the pH of the composition to between 2.45 and 4.6 [or less], wherein said acid selected from the group consisting of glycolic acid, lactic acid, succinic acid, malic acid, citric acid, acetic acid, and hydrochloric acid.
26. (Amended) A method for [preventing] the prophylaxis of lesions caused by a virus of the Herpesviridae or Poxviridae family, comprising topically applying a composition consisting essentially of 10% by volume ethanol and 0.6% by weight glycolic acid, wherein the pH of the composition to between 2.45 and 4.6, wherein said composition is applied during symptoms of pain, itching burning, or tingling.